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# RADIATION TREATMENT WITH TWICE A DAY FRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN HIGH GRADE ASTROCYTOMA

## A retrospective study

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**Abstract**

A consecutive series of 73 patients with high grade astrocytoma treated by surgery and postoperative radiotherapy was analysed. A total tumour dose of 60 Gy was delivered with either 2 Gy daily fractions (24 patients) or twice a day 1.5 Gy fractions, with a 4-hour-interval (49 patients). The analysis of survival with respect to patient variables showed that age and performance status were significant prognostic factors. As the type of fractionation was not randomly assigned, the comparison between the conventional schedule (CF) and the multifractionated schedule (MFD) was performed by means of a multivariate analysis adjusting for basic prognostic factors; CF proved to be significantly superior to MFD. The possible reasons for the disagreement between our results and the theoretical expectations in favour of MFD are discussed.

*Key words:* Brain neoplasms, high grade astrocytoma, radiation therapy, fractionation studies.

High grade astrocytoma (HGA) is the most common primary brain tumor of adults. Even though the outcome of treatment is still poor, postoperative radiotherapy has shown to prolong median survival significantly when compared to surgery alone (13, 22), with a clear dose-effect relationship (23). The addition to surgery and radiotherapy of adjuvant chemotherapy using nitrosoureas has been suggested to give better results (2), with an increase in long term survivors (10). However several trials have shown that only a slight gain can be obtained by chemotherapy, thus reported median survival still remains in the range of 8–12 months (2, 8, 10–12).

Among the several approaches that have been tested to achieve better results, misonidazole-sensitized radiotherapy (9, 11, 14) and fast neutron beams (7) have failed to yield any survival benefit up to now. Unconventional fractionations, especially the so-called 'multiple fractions per day' schedules (MFD), are also being explored. On a theoretical base, hyperfractionation (HF) and accelerated fractionation (AF), as defined by THAMES et coll. (21), could in some degree overcome 2 possible reasons for radioresistance of HGA, i.e. the presence of a large fraction of hypoxic cells and the rapid growth rate, the former by means of the larger number of fractions, as compared with conventional fractionation (CF), the latter by shortening the overall treatment time (5).

Despite the sound biological rationale, the results reported from studies of both types of multifractionation (AF and HF), are conflicting: DOUGLAS & WORTH (6) found a gain in survival in patients treated with HF, compared to historical controls; ANG et coll. (1) obtained 'encouraging' preliminary results with AF plus misonidazole in a non-randomized study. As far as randomized studies are concerned, no significant improvement could be shown by PAYNE et coll. (16) and SHIN et coll. (20) in patients treated with a rather low total dose HF schedule plus chemotherapy; on the contrary, FULTON et coll. (9) showed a significant gain in both time to progression and median survival in his study comparing HF (with or without misonidazole) to a control group, the results of which, however, seem unusually poor.

The present investigation is a retrospective analysis of clinical results in a consecutive series of patients treated with surgery and postoperative radiotherapy delivered by two different fractionation schedules, a conventional one and a twice a day fractionation, with 1.5 Gy per fraction. The latter is a regimen combining some aspects of both AF and HF, namely a shortened overall time and reduced

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**Table 1**

*Patient characteristics in CF and MFD fractionation groups*

| | CF | MFD | TOT |
|---|---|---|---|
| Age (years) | | | |
| 18–40 | 9 | 4 | 13 |
| 41–50 | 5 | 18 | 23 |
| 51–60 | 5 | 16 | 21 |
| 61–80 | 5 | 11 | 16 |
| Sex | | | |
| Female | 10 | 16 | 26 |
| Male | 14 | 33 | 47 |
| Histologic grade | | | |
| III | 13 | 31 | 44 |
| IV | 11 | 18 | 29 |
| Site and extension | | | |
| 1 lobe, frontal | 8 | 12 | 20 |
| 1 lobe, non frontal | 7 | 18 | 25 |
| More than 1 lobe | 9 | 19 | 28 |
| Interval from surgery to radiotherapy (days) | | | |
| ≤20 | 11 | 22 | 33 |
| >20 | 13 | 27 | 40 |
| Performance status-Order | | | |
| I | 11 | 15 | 26 |
| II | 7 | 20 | 27 |
| III | 6 | 14 | 20 |
| Performance status-Karnofsky | | | |
| 100–80 | 12 | 21 | 33 |
| 70–60 | 6 | 18 | 24 |
| 50–40 | 6 | 10 | 16 |
| Ambulatory status | | | |
| Yes | 24 | 21 | 45 |
| No | – | 28 | 28 |
| Total | 24 | 49 | 73 |
| Alive | 10 | 6 | 16 |

dose per fraction. The allocation of patients to either schedule was not randomized. The twice a day fractionation was our standard therapy and conventional fractionation was reserved for those non-hospitalized patients unable to support a twice a day schedule owing to non-medical reasons. This may have yielded some imbalance of prognostic factors between MFD and CF patients, but this possibility was taken into account in our statistical analysis.

## Material and Methods

The study group consisted of a consecutive series of 73 adult patients with a histologically confirmed diagnosis of malignant astrocytoma grade III or IV. All patients were given postoperative radiotherapy at the Department of Radiotherapy of the 'Ospedale di Circolo', Varese, from April 1979 to December 1984. Patients with recurrent or persistent tumours were excluded from our analysis, as well as a single patient who failed to complete treatment because of deterioration of his physical condition.

*Patient population.* Patient characteristics in CF and MFD groups regarding age, sex, histological grade, interval between surgery and radiotherapy, site and extension of tumour, performance status indexes and ambulatory status are summarized in Table 1. Mean age ± standard error (SE) of the whole population was 50.3±13.0 years. Tumours were classified as grade III or IV astrocytoma according to Kernohan's classification; the exceedingly high percentage of grade III cases (60.3%) may be ascribed to an incomplete referral of grade IV patients from the largest referring neurosurgical center. The performance status was recorded in each patient at the beginning of radiotherapy according both to the Karnofsky system and to the Order classification based on neurological functional status (Table 2) (15). As shown in Table 3, the Karnofsky score and the Order class were closely correlated.

**Table 2**

*Neuroperformance classification (Order)*

| Class | Definition |
|---|---|
| I | Intellectually and physically able to work; neurological findings minor or absent. |
| II | Intellectually intact and physically able to be at home, although nursing care may be required; neurological findings present but not a major factor. |
| III | Major neurological findings requiring hospitalization and medical care and supervision. |
| IV | Requires hospitalization and is in serious physical and neurological state. |

**Table 3**

*Performance status: correlation between Karnofsky score and Order class*

| Karnofsky | 100–80 | 70–60 | 50–40 |
|---|---|---|---|
| Order I | 24 | 2 | 0 |
| Order II | 8 | 18 | 1 |
| Order III | 1 | 4 | 15 |

*Treatment.* The type of surgical procedure ranged from macroscopically complete excision to minimal tumour removal, in either case, the resection was the largest allowed by the tumour site. As the extent of surgery could not be clearly defined in all cases, we did not examine this factor in our analysis. Chemotherapy was delivered following surgery in 16 patients, 11 of whom received BCNU; these patients were evenly distributed between CF and MFD groups (7 and 9 respectively) and, since chemotherapy is not expected to have a substantial impact on survival, this variable was left out.

The median interval from surgery to the beginning of radiotherapy was 21 days. Radiotherapy was delivered by two 10 MV X-rays parallel opposed fields, both fields treated each day, for a whole-brain total dose of 40–46 Gy, then up to a total dose of about 60 Gy to the tumour

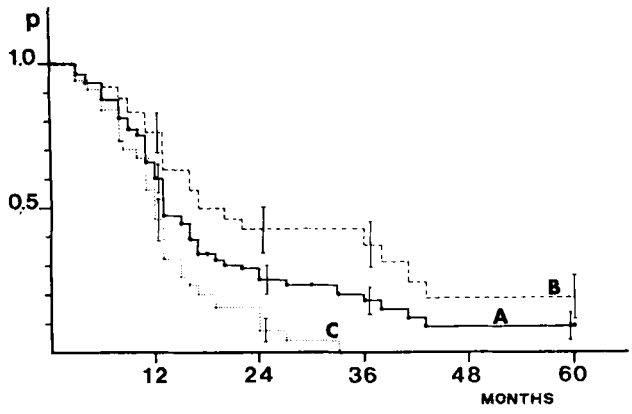


Fig. 1. Crude survival from time of surgery. P=probability of survival; A) whole group (73 pts.), B) 18–50 years old (36 pts.) and C) 51–80 years old (37 pts.).

bearing area with reduced fields. Twice a day fractionation was adopted whenever possible, with 1.5 Gy fractions given twice per day, 4 hours apart, over 4 weeks; this group included all the hospitalized patients (n=28) and nearly half of the ambulatory patients (n=21/45). Conventional fractionation (2 Gy daily fractions over 6 weeks) was adopted in the remaining out-patients (n=24), for non-medical reasons. As regards the dose delivered to the whole brain, in patients treated from 1979 to 1981 a range of 38–41 Gy was adopted, whereas patients treated from 1982 to 1984 received a higher dose, i.e. 43.5–46 Gy. On the other hand, the total dose was kept fixed at about 60 Gy in both periods, and was also quite similar in CF and MFD groups (mean±SE: 60.92 Gy±1.66 Gy and 60.08 Gy±1.70 Gy, respectively).

No patients received any further therapy after tumour progression, apart from steroid medication.

*Follow up*. After completion of radiotherapy all patients were followed up every 3 months; none of the 35 patients who underwent a post-treatment computerized tomographic scan showed any evidence of necrosis of normal brain tissue. At the time of the analysis (June 1986) 16 patients were still alive. All deaths were caused by tumour progression.

*Statistical analysis*. The only endpoint was survival from time of surgery. Actuarial survival curves were calculated using the life-table method. Possible prognostic factors were analysed, the respective groups being compared by means of the logrank test. Fractionation schedules were first compared by univariate analysis, then by a multivariate analysis adjusting simultaneously for the 2 major prognostic factors with a retrospective stratification as described by PETO et coll. (17).

## Results

Fig. 1 shows the actuarial survival curve for the whole series; median survival was 12.5 months and percentages of survivors ±SE at 1, 2 and 3 years were 60.2%±5.4%, 25.0%±5.2%, 17.9%±5.0% respectively. The univariate analysis did not show any prognostic significance of the following factors: sex, histologic grade, extension of tumour, interval from surgery to radiotherapy, whole-brain radiation dose and ambulatory status. When restricting the analysis to single-lobe tumours, the patients with frontal astrocytomas had significantly better prognosis than those with non-frontal ones (Table 4).

Age and performance status, according both to Karnofsky and to Order system, were identified as basic prognostic factors. A significant survival benefit was found in patients less than 50 years old (Fig. 1), and in patients with Order class I as compared with II+III (Fig. 2) as well as in patients with a score of 80–100 on the Karnofsky scale (Table 4). Age and Order class also showed significant prognostic trends in a more detailed analysis: after stratification into 4 age subgroups (18–40, 41–50, 51–60, 61–80 years) as well as considering each Order class apart (I vs. II vs. III), the T-test by PETO et coll. (17) gave trends of significant survival differences ($p<0.001$).

**Table 4**

*One-year survival by prognostic subgroups. (*=Logrank test: $p<0.05$)*

| Prognostic subgroups | 1-year survival (%) | ±SE (%) |
|---|---|---|
| Age (years) | | |
| 18–50 | *74.9 | 6.9 |
| 51–80 | *45.9 | 7.0 |
| Sex | | |
| Female | 65.4 | 8.9 |
| Male | 57.4 | 6.7 |
| Histologic grade | | |
| III | 63.6 | 6.9 |
| IV | 55.2 | 8.7 |
| Site and extension | | |
| 1 lobe, frontal | *68.4 | 10.3 |
| 1 lobe, non-frontal | *43.5 | 9.4 |
| 1 lobe, overall | 55.5 | 7.0 |
| More than 1 lobe | 67.8 | 8.5 |
| Interval from surgery to radiotherapy | | |
| ≤20 days | 48.5 | 8.0 |
| >20 days | 70.0 | 7.0 |
| Performance status-Order | | |
| I | *80.7 | 7.4 |
| II+III | *48.9 | 6.0 |
| Performance status-Karnofsky | | |
| 100–80 | *69.7 | 7.6 |
| 70–40 | *52.5 | 6.9 |
| Ambulatory status | | |
| Yes | 68.2 | 7.1 |
| No | 48.3 | 8.4 |
| Whole-brain radiation dose (Gy) | | |
| 38–41 | 57.1 | 7.9 |
| 43.5–46 | 63.9 | 7.7 |
| Overall | 60.2 | 5.4 |

With respect to fractionation, survival was significantly better in patients treated with CF than in MFD patients; at 1, 2 and 3 years, survival rates ±SE were 83.3%±7.4%, 40.6%±10.5%, 40.6%±10.5% for CF versus 48.9% ±6.6%, 18.3%±5.3%, 7.6%±4.0% for MFD patients (Fig. 3). As fractionation was not randomly assigned, we performed a multivariate analysis of fractionation adjusted by age and performance status; regarding the latter, the Order scale was used because it appeared to be better correlated with prognosis than Karnofsky scale. The multivariate analysis confirmed the significant advantage of CF over MFD (logrank test: $\chi^2=4.32$, $p<0.05$). The difference in favour of CF remained after excluding single-lobe frontal tumours and the slightly unbalanced distribution of tumour sites did thus not bias the results of the comparison.

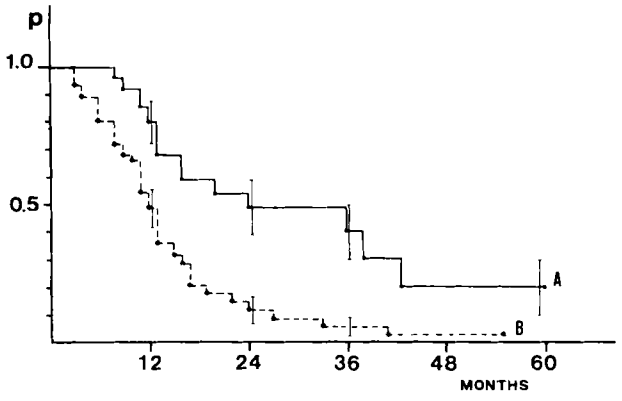


Fig. 2. Crude survival by performance status. P=probability of survival; A) Order class I and B) Order class II+III.

## Discussion

In our series of patients crude survival rate was similar to data reported in literature from most HGA studies; however our 3-year survival rate of 17.9%±5.0% seems quite high, which, at least in some degree, could be due to the high proportion of grade III astrocytomas. Apart from tumour grade, the distribution of patient characteristics was rather similar to what is usually reported. In our patients age and performance status were shown to be the most important variables for predicting survival, in accordance with most published studies (1, 2, 8–11, 14, 16, 22). Because of defective data, the extent of surgery and the amount of residual tumour could not be included in our analysis. However, it must be stressed that a consensus does not exist about the value of extended surgery: actually this factor did not exhibit a prognostic significance independent of other variables in the Cox regression analysis reported from the Brain Tumor Study Group (10).

The aim of our retrospective investigation was to identify any possible advantage given by MFD in the treatment of HGA, in terms of crude survival. Previous reports have given conflicting results (1, 6, 9, 16, 20). Our MFD schedule differed substantially from most schedules employed for brain tumours up to now, being a compromise between the so-called hyperfractionation and accelerated fractionation (21). Our results disagreed with the theoretical anticipations, as CF was found to be distinctly superior to MFD. This difference in favour of CF was confirmed in the retrospectively stratified analysis allowing for the unbalanced distribution of prognostic variables. Definitive conclusions cannot be drawn from our study, but its results suggest an unfavourable effect on survival of twice a day fractionation when a fraction size of 1.5 Gy is adopted. These results could contradict the anticipated advantages of MFD. However, it should be noted that MFD and CF patients were treated with a similar total dose (about 60 Gy), but with different fraction doses (1.5 vs. 2.0 Gy) and different overall treatment time (4 and 6 weeks respectively). At the present stage of knowledge, one cannot state with certainty the relevance of the overall treatment time for the probability of tumour control. The shorter treatment time should, however, be expected to work in favour of MFD, thus underlining the unfavourable behaviour of this group in our study.

Unconventional fractionations could give different effects in normal brain tissue compared with a conventional schedule given with the same total dose. Several tentative isoeffect models for central nervous system tolerance have been developed, all giving outstanding weight to the size of the dose per fraction. The mean values of 'brain tolerance unit' (BTU, according to PEZNER & ARCHAMBEAU (18)) differed significantly in two classes of fractionation (1 145±35 vs. 1 027±17 for CF and MFD respectively). As to the linear-quadratic model, on the assumption of an $\alpha/\beta$ value of 4.2 for human brain late damage (3, 19), RE values ('relative effectiveness per unit dose') as defined by DALE (4) were lower in twice a day fractiona-

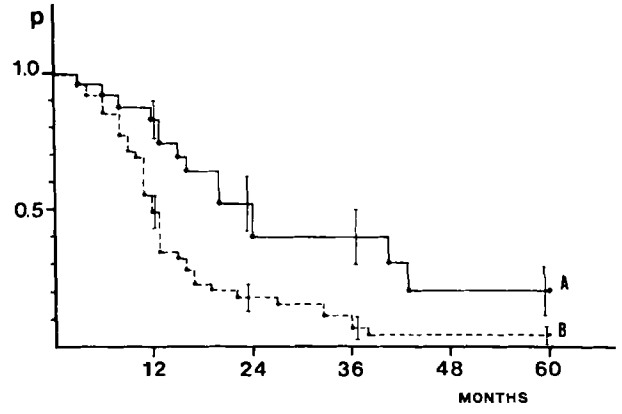


Fig. 3. Crude survival by type of fractionation. P=probability of survival; A) conventional fractionation (CF) and B) twice a day fractionation (MFD).

tion, as compared with CF: 1.38 vs. 1.47. If these isoeffect estimations are correct, one could expect some difference in late effects between CF and twice a day fractionation with 1.5 Gy fractions, provided that the total dose is kept fixed. This point could not be clarified in our study due to insufficient data concerning late effects. Nevertheless, since late brain tolerance is the dose-limiting factor in radiation therapy of HGA, we suggest that any fractionation schedule should be compared with conventional treatment using a total dose leading to the same probability of late damage, as tentatively predicted by isoeffect models. When using twice a day 1.5 Gy fractions, the total dose equivalent to 60 Gy given by CF (as to late tolerance only) is likely to be in the range of 65–75 Gy. Doses like these might be needed for revealing any potential therapeutic gain achievable by MFD. The use of doses higher than 60 Gy in multifractionated radiotherapy of HGA has been reported (9), but as far as we know, no definitive results have been published.

In conclusion, further studies will be required in order to establish the best fractionation in the radiotherapy of high grade astrocytomas; testing higher doses in hyperfractionated or partially hyperfractionated schedules seems advisable, provided that late brain damage is carefully evaluated.

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